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Susan LaMont
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

HELDIN et al.

Serial No.: 08/453,350 Group Art Unit: 1647

Filing Date: May 30, 1995 Examiner: C. Saoud

Title: RECOMBINANT PDGF A-CHAIN HOMODIMERS AND METHODS OF USE (AS AMENDED)

REPLY TO EXAMINER'S ANSWER

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INTRODUCTION

Appellants submit this reply brief on appeal in accordance with 37 C.F.R. §1.193(b)(1). An Examiner's Answer was mailed on April 9, 2001. In light of the record in this case and following arguments, Appellants respectfully request that the decision of the Examiner be reversed.

REMARKS

The Examiner has maintained the rejections of all pending claims (claims 25-27, 43-45 and 55-66) over Heldin et al., *Nature* (1986) 319:511-514 (hereinafter "Heldin"). For the reasons of record and those previously set forth in the Appellants' Brief on Appeal, claims 25-27, 43-45 and 55-66 are patentable over Heldin because there is no teaching, suggestion or motivation within this reference to support the assertions made by the Examiner. Furthermore, the claims are also patentable over Heldin for the reasons set forth in the declarations and other evidence of record.

Appellants address certain issues raised in the Examiner's Answer herein.

A) Appellants "Summary of the Invention" is not Deficient

The Examiner maintains that the Summary of the Invention in Appellants' Brief on Appeal is deficient because the specification fails to literally recite a "protein preparation that is free of other human proteins."

As required by 37 C.F.R. 1.192(a)(2), Appellants' Summary of their Invention properly contains a "concise explanation of the invention defined in the claims involved in the appeal... ." Here, the claims involved in the appeal are directed to PDGF protein preparations that are free of other human proteins. (See, *e.g.*, claim 1). Accordingly, pursuant to 37 C.F.R. 1.192(a)(2), the Summary of the Invention properly contained this claim language.

Furthermore, Appellants submit that the specification fully supports the claims as pending. The recitation "free of other human proteins" was first presented in an Amendment filed April 7, 1997. In that Amendment, Appellants noted that support could be found, for example, on page 13, lines 9-21 and in the Examples. Appellants also stated that no new matter was added as a result of these amendments. The Office did not then, and has not since, raised any objection to the pending claim language and the Examiner cannot, at this late date, suddenly object to such language.

Thus, because the claims are fully supported by the specification and because Appellants' are required to summarize the claims on appeal, the "Summary of the Invention" presented in the Appeal Brief was not deficient.

B. Heldin fails to disclose a protein preparation that is free of other human proteins and pathogenic viruses

The Examiner disagrees that Appellants were the first to produce a PDGF protein preparation free of other human proteins and/or pathogenic viruses. (Examiner's Answer, page 4). Indeed, the Examiner maintains that "the protein isolated by Heldin et al. appears to be highly pure and free of other human proteins, since there are no bands other than PDGF AA in the protein preparation which are visible after SDS PAGE and silver staining of the gel. It is well-known in the art that silver staining is one of the most highly sensitive methods of determining whether there are any protein contaminants in a preparation." (Office Action, pages 4-5, emphasis added).

In an attempt to bolster this argument, the Examiner also asserts that the language "free of other human proteins" does not mean free of "all human proteins" and, accordingly, absolute purity is not required by the claims. (Examiner's Answer, pages 10-11). The Examiner continues along this line of thought, maintaining that "[s]ince the claims do not encompass absolute purity, the preparation of Heldin meets the limitations of the claims. If the claims intend absolute purity, it is asserted that the claims are not enabled, because the preparation of a protein from a recombinant cell requires manipulation by a technician, which would ultimately result in contamination, which would not equate with absolute purity." (Examiner's Answer, page 11).

These assertions are irrelevant, illogical and unsubstantiated. First and foremost, the Examiner's focus on how the phrase "free of other human proteins" is interpreted is not relevant to the question of whether these claims are patentable. Rather, the relevant patentability inquiry is whether the cited reference teaches or suggests the claimed subject matter -- recombinantly-produced protein preparations that are free of other human proteins. For the reasons detailed above and in previous submissions to the Office, Heldin does not describe or suggest the claimed preparations. Simply put, proteins produced recombinantly in non-human cells will be free of other human proteins, while Heldin's preparations will not be free of other human proteins. (*See, e.g.*, Appeal Brief and Cousens and Betsholtz Declarations).

Thus, Heldin does not "meet the limitations" of the pending claims. The evidence

of record totally refutes the Examiner's conclusion that Heldin's protein preparation "appears" to be free of other human proteins. Furthermore, as required by law, this evidence of record is comparative in that it compares Heldin's preparation to the preparations claimed by Appellants. (*See, also,* Section C, below detailing the adequacy of the declarations). Again, the "evidence" relied on by the Examiner in asserting that Heldin anticipates the pending claims is silver staining data. Appellants have conclusively demonstrated that a single silver stained band is not evidence of homogeneity (*e.g.,* the absence of other human proteins). It is known by persons of ordinary skill in the art of protein chemistry that there are inherent limits in the ability of the SDS-PAGE/silver staining method used in Heldin to detect the presence of protein. In particular, contaminating proteins and/or viruses present in the preparation may escape detection because (1) they are not stained or are only weakly stained, due to a wide variety of factors, including: (a) particulars of amino acid sequence or (b) secondary or tertiary structure of the polypeptide chain, or (c) variability in staining conditions; or (2) because they are of low molecular weight and have diffused out of the gel; or (3) because they are present in amounts below the threshold limit of detection. (See, *e.g.*, Cousens Declaration, paragraphs 4 and 5). Thus, the Examiner's unsubstantiated statement that silver staining is "well-known" to be a "highly sensitive" measure of homogeneity is entirely contradicted by the evidence of record.

Likewise, the fact that only a single amino acid sequence was obtained for the reference protein preparation would not be understood by a protein chemist of ordinary skill as conclusive evidence of a homogeneous preparation. Proteins with "blocked" N-terminus amino acids (*i.e.*, residues which are incapable of reacting with the sequencing reagents) will not be detected. Notably, many eucaryotic proteins, including some human proteins, are "blocked." (Cousens Declaration, paragraph 6). It is, therefore, continued error for the Examiner to rely on this observation as evidence that protein preparation of Heldin is homogenous. (See, Appeal Brief, page 13).

Appellant's disclosure is the only document of record that describes and demonstrates production of a PDGF protein product that is free of other human proteins. The art and the record is clear -- silver staining does not (and, in fact, cannot) reveal

contamination that is inherent when isolating a naturally, non-recombinantly produced product.

Even assuming, for the sake of argument only, that Appellants' protein preparations were required to be "absolutely" pure, the record establishes that the claims are both enabled by the specification as filed and, additionally, define a protein preparation that is distinct from Heldin's isolated protein preparation. With regard to enablement, Appellants first note that the Examiner is prohibited from issuing a new rejection (*i.e.* enablement) in an Examiner's Answer. (See, 37 C.F.R. 1.193(a)(2)). The Examiner cannot now, at this late stage in prosecution, question specific claim recitations and newly raise enablement issues. In any event, the specification fully enables the pending claims, even under the Examiner's strained interpretation that absolute purity is required. In particular, the specification teaches purification techniques from non-human cells of recombinantly produced PDGF. Recombinant purification schemes can be automated, avoiding all human contact. Even when human technicians perform some or all manipulations, they can (and do) wear gloves, masks and the like which eliminate any transfer of human proteins. Such precautions are regularly taken when dealing with recombinant protein and/or nucleic acid preparations. In direct contrast, proteins (like Heldin's) which are isolated from human cells will not be free of other human proteins, no matter how they are isolated or who isolates them. Accordingly, Heldin cannot anticipate the pending claims no matter how the recitation "free of other human proteins" is interpreted.

In sum, Appellants have demonstrated that the claimed protein preparation are patentably distinguishable from Heldin's protein preparation no matter how the claims are interpreted. The claimed PDGF preparations are inherently different than Heldin's preparations and are obtained by inherently different methods than described or suggested by Heldin.

C. Declaratory Evidence of Record Has not been Adequately Considered

The Examiner summarily dismisses the declaration evidence of record on the grounds that it is allegedly not "comparative evidence." Appellants strongly disagree

with this allegation. The Betsholtz Declaration, for example, clearly compares Heldin's preparation with the claimed preparations when noting that "it is a virtual certainty that trace amounts of [other] human proteins were present in the ... preparations [of Heldin] that were not detected by these methods." (Betsholtz Declaration, paragraph 5). Similarly, the Cousens Declaration pointedly and purposely contrasts isolated protein preparations (Heldin) against recombinantly produced preparations of the same protein (the claimed invention) and, as a result of this direct comparison, finds that:

> "The recombinant methods of producing human PDGF-A chain described in the patent application, on the other hand, results in a preparation free of human protein contaminants and devoid of contaminating human viruses. As explained in Dr. Betsholtz's previous Declaration, this is because the only human structural gene present in the recombinant plasmids is the gene encoding human PDGF. It would not be possible to produce preparations having such purity without the gene encoding PDGF and Heldin does not describe the gene or recombinant methods for producing PGDF A-chain." (Cousens Declaration, paragraph 7).

The evidence of record is clearly comparative as it directly compares and contrasts the claimed protein preparations with those disclosed in Heldin. Accordingly, this declaratory evidence must be given fair weight and consideration. *In re Alton,* 37 USPQ2d 1578 (CAFC 1996). Moreover, when properly considered, the comparative evidence of record establishes that the claimed invention is not anticipated, either inherently or expressly, by Heldin.

D. The Evidence of Record Has Not Been Adequately Rebutted

In her Answer, the Examiner takes issue with Appellants' statement that the Examiner failed to consider evidence of record and substituted her own personal knowledge in place of that presented by expert Declarants:

> "This assertion is unfounded in that all evidence and arguments have been carefully considered, and upon consideration of all evidence and arguments, the Examiner arrived at a conclusion that differed from that of Appellants. This does not equate to 'substituting her own personal knowledge' and no such 'personal knowledge' have been referenced in the grounds of rejection." (Examiner's Answer, page 6).

The facts are clear that the Examiner has done much more than simply arrive at a different conclusion than Appellants. In fact, the Examiner has arrived at a different conclusion than Appellants; a different conclusion than several expert Declarants; and a different conclusion than the authors of various publications and texts. Moreover, no reasons or evidence is provided in support of these "different conclusions." In short, the Examiner's conclusions can only be based on her own personal knowledge and opinions.

Examples of improper substitution of personal knowledge for the evidence of record can be found throughout the Examiner's Answer. For instance, in interpreting the claims, the Examiner asserts that all recombinant protein preparations will necessarily be contaminated with human proteins because of human contact. This is inaccurate, as human technicians regularly perform molecular biological manipulations without resulting in contamination. Furthermore, in dismissing Appellants evidence (*e.g.*, Declarations and the Kornberg reference) establishing that silver staining is not conclusive evidence as to contamination with other human proteins, the Examiner asserts that it is "well-known in the art that silver staining is one of the most highly sensitive methods for determining whether there are any protein contaminants in a preparation" and that Heldin's preparation would "highly unlikely to be contaminated with virus." (Examiner's Answer, pages 4-5). No references are cited supporting the proposition that silver staining is the most highly sensitive method or that contamination of conditioned medium would be unlikely. Additionally, it is asserted that it would have been obvious to "dialyze a composition eluted from an HPLC column" to obtain the compositions of claims 55-57. (Examiner's Answer, pages 4 and 5). The Examiner has presented absolutely no evidence, references or declarations to support these (and other) assertions and has presented no evidence that rebuts Appellants' ample comparative evidence.

Indeed, the Declarations and other evidence of record comparing Heldin-type preparations with recombinantly-produced preparations all come to the same conclusion -- Heldin's preparations contain human protein contaminants while the claimed preparations are free of such other human proteins. In the face of Appellants' declaratory and other evidence establishing that (1) silver staining is entirely <u>insufficient</u> to determine contamination; (2) viral contamination of isolated proteins is likely; and (3) there is no

motivation in the cited reference to arrive at the claims 55-57, Appellants can only conclude that the Examiner has failed to properly consider the facts and conclusions presented by experts in the field and is substituting personal knowledge for that of expert Declarants and published references. This is not permitted.

When a rejection is based on facts within the personal knowledge of the Examiner, the data relied upon should be stated as specifically as possible, and the reference must be supported, when called for by the applicant, by an affidavit from the Examiner. MPEP 2144.03. Such an affidavit is subject to contradiction or explanation by the affidavits of the applicant and other persons. 37 C.F.R. 1.104(d)(2). The Examiner has so far failed to provide such an affidavit. Absent such an affidavit, it is entirely improper for the examiner to maintain the rejections of any of the pending claims. Further, by failing to provide the affidavit, Appellants are denied any opportunity to contradict or explain the facts relied on by the Examiner, or the conclusions based on those facts, which is his right under 1.104(d)(2).

E. The Claimed Protein Preparations are Patentably Different than Heldin's

As an extension of the allegation that the evidence of record is not "comparative" evidence, the Examiner maintains that Appellants have not established that there is a patentable difference between their protein preparations and those of Heldin. (Examiner's Answer, page 13 and cases cited therein).

The law and the facts plainly contradict the Examiner's position. By definition, pure materials necessarily differ from *less* pure or impure materials and, if the latter are the only ones existing and available as a standard of reference. The "pure" materials are "new" with respect to them whether or not the claimed pure materials have the same usefulness or assortment of properties as the impure materials of the prior art. *In re Bergstrom,* 166 USPQ 256, 262 (CCPA, 1970). Indeed, the Board itself has recognized that the purity of a preparation can be used to impart patentability over prior art referenced disclosing heterogeneous mixtures. See, e.g, *Ex parte Stern*, 13 USPQ2d, 1379 (BPAI). (See, Appeal Brief). Appellants further note that *Ex parte Stern* is a more recent decision than the cases cited by the Examiner and, consequently, better reflects the

known differences between isolated and recombinantly-produced proteins.

As detailed above, Appellants have presented ample comparative evidence establishing the differences between their preparations and those of Heldin. The claimed preparations are different both in how they are produced and, moreover, in their homogeneity. Unlike Heldin's protein preparation, Appellants protein preparation is recombinantly produced. Recombination production necessarily results in a preparation that is free of other human proteins and pathogenic viruses. Because the protein preparation claimed by is free of other human proteins, it is patentably distinct from the preparation taught in Heldin, which necessarily contains other proteins.

F. Obviousness has not been Established

Contrary to the Examiner's continued insistence, nowhere does Heldin teach or suggest the invention of claims 55-57. The Examiner acknowledges that Heldin is "not clear as to whether the purified composition was in a pharmaceutically acceptable carrier prior to the final gel analysis." (Examiner's Answer, page 5). However, for the reasons detailed above, it is equally clear that Heldin fails to teach or suggest the claimed purified composition *per se* as this reference does not teach recombinantly-produced PDGF preparations that are free of other human proteins.

The properties of the claimed protein preparations are precisely defined - in the claims themselves, not in the art. To somehow import those properties into hypothetical preparations and then to conclude that the hypothetical preparations would have exactly the same properties as the claimed PDGF preparations involves, at the very least, prohibited hindsight reconstruction.

CONCLUSION

For the reasons state above, Appellants respectfully submit that the pending claims define an invention which is nonobvious over the art cited by the Examiner and fully enabled by the specification.

Accordingly, Appellants request that the rejection of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed

claims can proceed to allowance.

Please direct all further communications in this application to:

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Respectfully submitted,

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